IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

PURDUE PHARMA PRODUCTS L.P., NAPP PHARMACEUTICAL GROUP LTD., BIOVAIL LABORATORIES INTERNATIONAL SRL, and ORTHO-MCNEIL, INC.,	)	
Plaintiffs,	)	C.A. No. 07-255-JJF
v.	)	
PAR PHARMACEUTICAL, INC. and PAR PHARMACEUTICAL COMPANIES, INC.,	)	**PUBLIC VERSION**
Defendants.	)	

SUPPLEMENTAL DECLARATION OF ROBERT E. COLLETTI IN SUPPORT OF DEFENDANTS' REPLY CLAIM CONSTRUCTION BRIEF

Of Counsel:
Daniel G. Brown
Wilson Sonsini Goodrich & Rosati, PC
1301 Avenue of the Americas, 40th Floor
New York, NY 10019
212-999-5800

Ron E. Shulman
Wilson Sonsini Goodrich & Rosati, PC
650 Page Mill Road
Palo Alto, CA 94304

Nicole W. Stafford
Wilson Sonsini Goodrich & Rosati, PC
900 South Capital of Texas Highway
Las Cimas IV, Fifth Floor
Austin, TX 78746-5546

Dated: August 22, 2008

Frederick L. Cottrell, III (#2555)
Cottrell@rlf.com
Steven J. Fineman (#4025)
Fineman@rlf.com
Richards, Layton & Finger P.A.
One Rodney Square
P.O. Box 551
Wilmington, DE 19899
(302) 651-7700

Attorneys for Defendants Par Pharmaceutical, Inc. and Par Pharmaceutical Companies, Inc.

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

PURDUE PHARMA PRODUCTS L.P., NAPP PHARMACEUTICAL GROUP LTD., BIOVAIL LABORATORIES INTERNATIONAL SRL, and ORTHO-MCNEIL, INC.,	Case No. 07-255-JJF (Consolidated)
Plaintiffs,	
v.	
PAR PHARMACEUTICAL, INC. and PAR PHARMACEUTICAL COMPANIES, INC.,	
Defendants.	

SUPPLEMENTAL DECLARATION OF ROBERT E. COLLETTI IN SUPPORT OF DEFENDANTS' REPLY CLAIM CONSTRUCTION BRIEF

I, Robert E. Colletti, declare pursuant to 28 U.S.C. § 1746 that:

1. I am a partner with the law firm of Frommer Lawrence & Haug LLP located at 745 Fifth Avenue, New York, New York 10151 and am counsel to Par Pharmaceutical, Inc. and Par Pharmaceutical Companies, Inc., (jointly "Par") in this action.

2. I make the following supplemental declaration in support of Defendants' Reply Claim Construction Brief.

3. Exhibit 1 is a true and correct copy of S. Venkatraman et al., *An Overview of Controlled Release Systems*, in HANDBOOK OF PHARMACEUTICAL CONTROLLED RELEASE TECHNOLOGY, 431-463 (Donald L. Wise ed., 2000).

I declare under penalty of perjury that the foregoing is true and correct.

Date: July 2, 2008

Robert E. Colletti

Robert E. Colletti

IN THE UNITED STATES DISTRICT COURT
DISTRICT OF DELAWARE

CERTIFICATE OF SERVICE

I hereby certify that on August 22, 2008, I electronically filed the foregoing document with the Clerk of Court using CM/ECF which will send notification of such filing(s) and Hand Delivered to the following:

Jack B. Blumenfeld, Esquire
Rodger D. Smith II, Esquire
Morris, Nichols, Arsht & Tunnell LLP
1201 North Market Street
P.O. Box 1347
Wilmington, DE 19899-1347

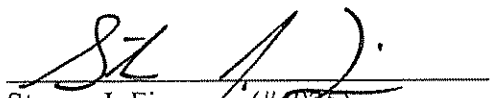
Richard D. Kirk, Esquire
The Bayard Firm
222 Delaware Avenue, Suite 900
P.O. Box 25130
Wilmington, DE 19899-5130

Mary W. Bourke, Esquire
Conolly Bove Lodge & Hutz LLP
The Nemours Building
1007 North Orange Street
P.O. Box 2207
Wilmington, DE 19899

I hereby certify that on August 22, 2008, I have sent by Electronic Mail, the foregoing document to the following non-registered participants:

Robert J. Goldman, Esquire
Ropes & Gray LLP
525 University Avenue
Suite 300
Palo Alto, California 94310

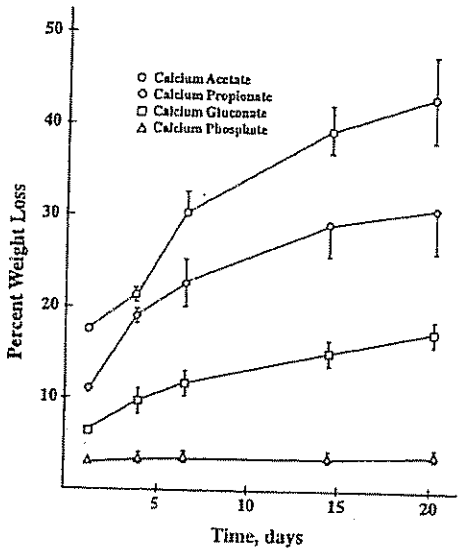
Richard A. Inz
Sona De
Ropes & Gray LLP
1211 Avenue of the Americas
New York, New York 10036



Steven J. Fineman (#4025)
Richards, Layton & Finger, P.A.
One Rodney Square
P.O. Box 551
Wilmington, Delaware 19899
(302) 651-7700
fineman@rlf.com

EXHIBIT 1

Handbook of Pharmaceutical Controlled Release Technology



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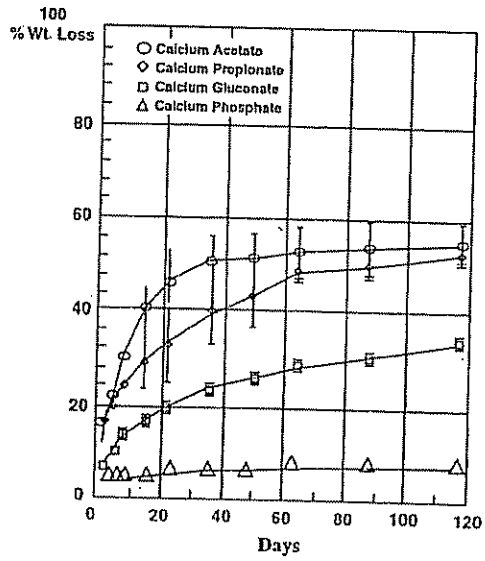

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edited by

Donald L. Wise

Handbook of Pharmaceutical Controlled Release Technology

executive editor
Donald L. Wise
Cambridge Scientific, Inc.
Cambridge, Massachusetts

associate editors

Lisa Brannon-Peppas
Biogel Technology, Inc.
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Debra J. Trantolo
Cambridge Scientific, Inc.
Cambridge, Massachusetts

Gary E. Wnek
Virginia Commonwealth University
Richmond, Virginia

Michael J. Yaszemski
Mayo Clinic
Rochester, Minnesota

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An Overview of Controlled Release Systems

S. Venkatraman, N. Davar, A. Chester, and L. Kleiner
ALZA Corporation, Mountain View, California

I. INTRODUCTION

The term *drug delivery* covers a very broad range of techniques used to get therapeutic agents into the human body. The limitations of the most obvious and trusted drug delivery techniques, those of the ingested tablet and of the intravenous (IV)/subcutaneous/intramuscular (IM) injections, have been recognized for some time now. The former delivers drug into the blood only through the hepatic system, and hence the amount in the bloodstream may be much lower than the amount formulated into the tablet (i.e., it has low bioavailability); furthermore, liver damage is an unfortunate side effect of many soluble tableted drugs. The injection mode of delivery can be used to deliver any size of drug molecule and is versatile in this regard, but it suffers from the obvious disadvantage of being invasive and painful, and the less obvious disadvantage of shortness of duration (for drugs with short half-lives). To overcome some of these limitations, other modes of delivery of drugs into the body were investigated, beginning in the early 1970s. Transdermal (through the intact skin), transmucosal (through the intact mucosa of the mouth, intestine, rectum, vagina, or nose), transocular (through the eye), transalveolar (inhalation, through lung tissue), implantable (subcutaneous and deeper implants, delivery into surrounding tissue), and injectable (IM or subcutaneous) modes of delivery have all been explored extensively over the last 25 years, with varying degrees of commercial and therapeutic success. Of the above modes, the transdermal, transmucosal (specifically intestinal), transocular, injectables and the subcutaneous implant have found varying degrees of commercial acceptance. Of the rest, the inhalation route appears promising for a limited class of agents and at least three companies have products in advanced clinical trials. In the next 5 years, this route of administration is very likely to become acceptable to patients and hence commercially successful.

Currently, two other modes of injectable drug delivery are receiving increased attention. One focuses on the use of nanoparticles for delivering DNA or genes to cells for transfection. These particles have the unique ability to be taken up by targeted cells via various transcellular entry mechanisms. Another mode is needleless (and hence painless) injectables, which are being investigated by at least two companies. These approaches are in feasibility or early clinical trials.

The common theme underlying these delivery modes is increased therapeutic efficiency as well as increased patient compliance. The common key ingredient of all these technologies is polymeric material. In this chapter we focus on the demands made on the polymer material, which is often the component that controls drug delivery

A. Drug Delivery Technologies

The main focus of this chapter will be four delivery modes: oral controlled release, transdermal, implantable, and particulate drug delivery. As mentioned above, all four modes have found commercial acceptance to varying degrees. The thrust of this chapter will be on the polymeric component and the requirements that each mode of delivery places on the polymer component. As can be imagined, the polymeric component must not only satisfy the design criteria for each mode of delivery, but also its toxicological and manufacturing requirements. Innovations in polymers drive improvements in these delivery technologies; therefore, each section will highlight the need for polymer improvements.

Regardless of the delivery mode, the polymer in each instance is required to perform a set of functions. To understand these functions, it is instructive to review the features and some of the shortcomings of the most popular forms of drug delivery, i.e., oral tablets and intravenous injections. In broad terms, these are summarized below as follows:

1. *Tablets*
    1. All drugs enter the main circulation via the liver; a portion of the delivered drug is metabolized. In addition, for certain drugs, liver toxicity is an issue.
    2. Drugs are typically absorbed in the stomach and in the small intestine (SI), where pH effects can influence extent of delivery.
    3. For drugs with short half-lives, duration of action is limited to the maximum transit time through the stomach and SI, approximately 6 h.
    4. The delivery profile typically has "peaks" and "valleys," i.e., fast onset followed by rapid decay. Constancy of drug levels in blood is rarely achieved
    5. There is a low level of patient compliance, i.e., patients forget to take the required dose at the correct time.

2. *Intravenous Delivery*
    1. There is no metabolism by the liver.
    2. Duration of action of a drug is determined solely by clearance rates for the drug; no control is possible (except for infusion control).
    3. Macromolecules can be delivered.
    4. The method is invasive and often painful, and therefore is not suitable for chronic indications.

Thus, alternative drug delivery modalities are needed to address the above shortcomings. The most important shortcomings are the duration of action and its control, by which is meant not only extended release of drug into the bloodstream, but also controlled release, i.e., achieving the desired plasma profile for the drug. In addition, the alternative modality must be acceptable to the patient (noninvasive) and must increase the level of patient compliance. There are also pharmacoeconomics and quality-of-life issues to be addressed.

Therefore, what the polymer is required to do, in these alternative drug delivery approaches, is to extend and control the release of the drug into the bloodstream via the various portals of entry (skin, oral mucosa, etc.). This is true of all modalities, except those where external fields are used to modulate drug delivery, such as iontophoresis (covered elsewhere in this book) and sonophoresis. The primary role of the polymer is diffusional control of active agents, and the secondary role is disintegration or dissolution control of the dosage form employed.

For reasons of editorial space, we will not be able to cover extensively the fields of buccal, rectal, or vaginal drug delivery, each of which is an active area of research. References to some of these concepts will be made in Section V.

B. Commercialized Technologies

As mentioned above, the transdermal delivery mode (commonly referred to as "patches") and controlled release orals are perhaps the most successful alternative delivery modes. Because of their similarity to bandages, transdermals found easy acceptance with patients. The duration of action of the first patch introduced (Transderm-Scop® developed by ALZA Corporation for Novartis Co. in 1981) was 72 h, easily surpassing the capability of existing tablets (Dramamine®) to provide continuous relief from sea or air sickness. The next type of transdermal introduced was for nitroglycerin delivery, and it also found immediate acceptance. Several companies introduced nitroglycerin transdermals, examples being Transderm-Nitro®, Nitro-Dur®. The duration of action was 24 h. With the introduction of Estraderm® by the then Ciba-Geigy Corporation, 3.5 days of delivery was achieved. Since then, we have seen the introduction of 7-day systems (Catapres TTS® for clonidine delivery, Climara® and FemPatch® for estradiol delivery). The transdermal market witnessed a surge in the early 1990s when the first nicotine patches were introduced for smoking cessation. Since then, the overall market has climbed to over $1 billion per annum for this mode of delivery.

Controlled release orals enjoy a large share of the drug delivery marketplace as well. Extended release dosage forms were introduced fairly early, but since these dosage forms do not strictly controlled drug delivery, they will not be discussed here (with the exception of dissolution-controlled delivery, Section II.A). The earliest from of controlled release oral dosage form was the osmotic tablet, developed by ALZA Corporation, for controlled delivery of phenylpropanolamine. This early product has been succeeded by several ethical pharmaceutical products, the most successful introduction being that of Procardia XL® by Pfizer: this product delivers a calcium channel blocker (CCB), nifedepine, in a controlled manner for 24 h using ALZA's proprietary osmotic tablet technology. To date, this technology is the most successful oral controlled release technology with about $2 billion of the total $6.2 billion in annual revenues for oral controlled release (CR) products. Other commercialized oral delivery technologies include R.P. Scherer's Zydis® (rapid-dissolve) and Elan Corporation's SODAS®, PRODAS®, and IPDAS® technologies. Of these, Zydis is not, strictly speaking, a controlled release technology, and it should be treated in the same manner as extended release branches of non-CR drug delivery technology. By our estimate, the CR share of the oral drug delivery market is about $3.5 billion—still much larger than the closest competing technology, transdermal delivery.

The other commercialized technology is implants. This delivery mode had about $1 billion in sales in 1996, largely from Norplant® (contraception), Atrisorb® and Atridox® from Atrix (dental implants for caries). Polymers play a large role in this technology as well, and we will explore this in detail in Section IV.

C. Technologies in Development

There are some CR technologies in various stages of development that have yet to see the marketplace. Noteworthy among these are controlled release via the alveoli (inhalation CR), controlled release via buccal tissue (buccal CR), and controlled release using microparticles or nanoparticles (particulate CR). The last named could have any of several modes of entry into the body. The most common mode of delivery for microparticles is as injectables (where the

product Lupron Depot® is a commercial success), the nasal mucosa and the gastrointestinal (GI) tract being the other two routes. While discounting extended duration nasal sprays for congestion as being an extended rather than a controlled release system, it must be said that truly controlled release products in this category are still in the research or early clinical phase. Inhalation CR is now being pursued by three or four major companies, with Inhale Therapeutic Systems and Aradigm Corporation in the lead with products in phase II or phase III clinicals, and the Dura Corporation concentrating on delivery to the upper lung (local delivery). Whether the inhalation products being developed are strictly controlled release products is debatable; however, their potential for displacing injections as a route for administering important new therapeutic entities (proteins and peptides) is beyond any debate. In any event, the role of polymers in the delivery of inhalation products is clearly peripheral rather than central, and therefore these products will not be discussed. While polymers do play a central role in buccal controlled release products, products are still in pre-clinical or phase I, with the 3M Company finding it relatively difficult to market its proprietary buccal platforms (as of 1998, no partner deals have been announced for its CyDot® transmucosal delivery (TMD) technology). Theratech (now part of Watson Pharmaceuticals) is the other major player in this arena, and has announced a *peptide* development agreement with Eli Lilly for an undisclosed peptide. Therefore, in Section V, we will concentrate on particulate drug delivery, since polymers do play a central role in this technology, and products have either been commercialized or are likely to be commercialized soon.

D. Synthetic vs. Natural Polymers

Natural polymers can be defined for our purposes as polymers derived from natural sources, such as cellulose. In the broadest sense, sources of such polymers may include animals (bovine collagen, chitosan) and plants (cellulose); recently, polymers that are identical to or similar to those occurring in the human body have also received closer attention. Examples are poly(lactic acid), poly(glycolic acid), and hyaluranic acid. The naturally occurring type of polymer continues to be expensive and therefore is indicated for use only when stringent biocompatibility is required, such as in long-term implants. Animal-derived polymers have found limited use in drug delivery systems, although they have been used extensively in applications such as wound healing. Plant-derived polymers have been used extensively in drug delivery systems; hydroxy derivatives have in particular, being found to be benign for oral delivery. In general, synthetic polymers have found far wider application in drug delivery systems, for reasons that will be made clearer in the following sections.

E. Some General Toxicological Considerations

The potential adverse effects of polymers must be evaluated prior to testing a drug delivery system in humans. Potential adverse effects may result from contact with the polymer or from leachables such as residual monomers, reactive agents, or processing additives. The effects of polymers or extracts will be dependent on unique chemical characteristics and the amount (or dose) of polymer/extract administered. There should be an evaluation of whether the polymer is in direct or indirect contact with the drug-containing component of the system or with tissues of the patient. These evaluations will assist in the determination of the types of safety assessments that may be required during the various stages of the development process. To assist in the selection of materials, a review of the manufacturer's and published scientific literature should be conducted to gather clinical and nonclinical safety information. If necessary, in vivo and in vitro tests are used to evaluate the biocompatibility of the polymer and/or extract and of

the drug delivery system, ensuring the safety of the system. In vitro studies should be conducted prior to initiating in vivo studies. Cytotoxicity tests are simple, rapid in vitro procedures that can provide predictive information on in vivo biocompatibility of polymeric materials (1). In vivo tests can then be conducted on the polymer and the drug delivery system.

II. ORAL DRUG DELIVERY SYSTEMS

Among all routes of administration, the oral route has been most popular and successful. This is, in part, because of the inherent simplicity of both the oral route and oral delivery systems. On the other hand, the oral route is constrained by short and variable GI transit time, first-pass metabolism, limited absorption in the lower part of the GI tract, and the size of the system.

A. Designs

Oral controlled delivery systems can be broadly divided into following categories, based on their mechanism of drug release:

1. Dissolution-controlled release
   a. Encapsulation dissolution control
   b. Matrix dissolution control
2. Diffusion-controlled release
   a. Reservoir devices
   b. Matrix devices
3. Ion exchange resins
4. Osmotic controlled release
5. Gastroretentive systems

1. Dissolution-controlled release

Dissolution-controlled release can be obtained by slowing the dissolution rate of a drug in the GI medium, incorporating the drug in an insoluble polymer, and coating drug particles or granules with polymeric materials of varying thickness. The rate-limiting step for dissolution of a drug is the diffusion across an aqueous boundary layer. The solubility of the drug provides the source of energy for drug release, which is countered by the stagnant-fluid diffusional boundary layer (2). The rate of dissolution (dm/dt) can be approximated by Eq. 1.

$$\frac{dm}{dt} = \frac{ADS}{h} \tag{1}$$

In Eq. 1, S is the aqueous solubility of the drug, A is the surface area of the dissolving particle or tablet, D is the diffusivity of the drug, and h is the thickness of the boundary layer.

Some examples of drugs with limited dissolution rate include digoxin, griseofulvin, salicylamide (3), and nifedipine (Adalat Retard tablet) (2). Unfortunately, this approach does not allow for a constant release rate because the surface area (A) changes with time. Also, the solubility (S) of the drugs, which are weak acids or bases, is affected by the variable pH of the GI tract.

Drug delivery using rate of dissolution as a controlled release mechanism can be achieved by *encapsulation* of a drug–polymer matrix with a relatively insoluble polymeric membrane. The coated beads can be compressed into tablets or capsulated, as was done with the Spansule® products (4). Since the time required for the membrane coat to dissolve is a function of membrane

thickness, granules with varying thicknesses can be employed to achieve sustained release of the drug. Examples of drugs delivered in this manner include antispasmodic–sedative combinations (5), phenothiazines (6,7), and anticholinesterase agents (8).

One of the most common approaches used to achieve sustained release is to incorporate a drug in a hydrophobic matrix such as wax, polyethylene, polypropylene, and ethylcellulose; or a hydrophilic matrix such as hydroxypropylcellulose, hydroxypropylmethylcellulose, methylcellulose, and sodium carboxymethylcellulose. The rate of drug availability is controlled by the rate of penetration of the dissolution fluid into the matrix. It depends on the porosity of the compressed structure. In the case of a water-soluble drug in a hydrophobic matrix, the rate of drug availability.

2. *Diffusion-Controlled Release*

Diffusion of a drug molecule through a polymeric membrane forms the basis of these controlled drug delivery systems. Similar to the dissolution-controlled systems, the diffusion-controlled devices are manufactured either by encapsulating the drug particle in a polymeric membrane or by dispersing the drug in a polymeric matrix. Unlike the dissolution-controlled systems, the drug is made available as a result of partitioning through the polymer. In the case of a reservoir type diffusion-controlled device (9), the rate of drug released (dm/dt) can be calculated using Eq. 2.

$$\frac{dm}{dt} = ADK\frac{\Delta C}{\ell} \tag{2}$$

In Eq. 2, A is the area, D is the diffusion coefficient, K is the partition coefficient of the drug between the drug core and the membrane, ℓ is the diffusional pathlength, and ΔC is the concentration difference across the membrane. In order to achieve a constant release rate, all of the terms on the right side of Eq. 2 must be held constant. It is very common for diffusion-controlled devices to exhibit a non-zero-order release rate due to an increase in diffusional resistance and a decrease in effective diffusion area as the release proceeds.

Another configuration of diffusion-controlled systems includes matrix devices, which are very common because of ease of fabrication. Diffusion control involves dispersion of drug in either a water-insoluble or a hydrophilic polymer (10–13). For instance, bupropion hydrochloride (Zyban®, Glaxo Wellcome) is formulated using carnuba wax and hydroxypropylmethylcellulose (13). The release rate is dependent on the rate of drug diffusion through the matrix but not on the rate of solid dissolution. Equation 3 describes the amount of drug released from the systems as derived by Higuchi (14):

$$Q = \left[\frac{D\epsilon}{\tau}(2C - \epsilon S)St\right]^{1/2} \tag{3}$$

In Eq. 3, Q is the amount of drug released per unit surface area, D is the diffusion coefficient of the drug in the release media, ϵ is the porosity, τ is the tortuosity of the matrix, S is the solubility of the drug in the release media, and C is the concentration of the drug in the tablet.

3. *Osmotically Controlled Release*

In the early 1970s, Theeuwes et al. (15) developed an elementary osmotic pump (EOP) to achieve controlled drug delivery. The delivery of the drug from the system is controlled by solvent influx across a semipermeable membrane, which in turn carries the drug outside through a laser-drilled orifice. The osmotic and hydrostatic pressure differences on either side of the semipermeable membrane govern fluid transport into the system. Therefore, the rate of drug

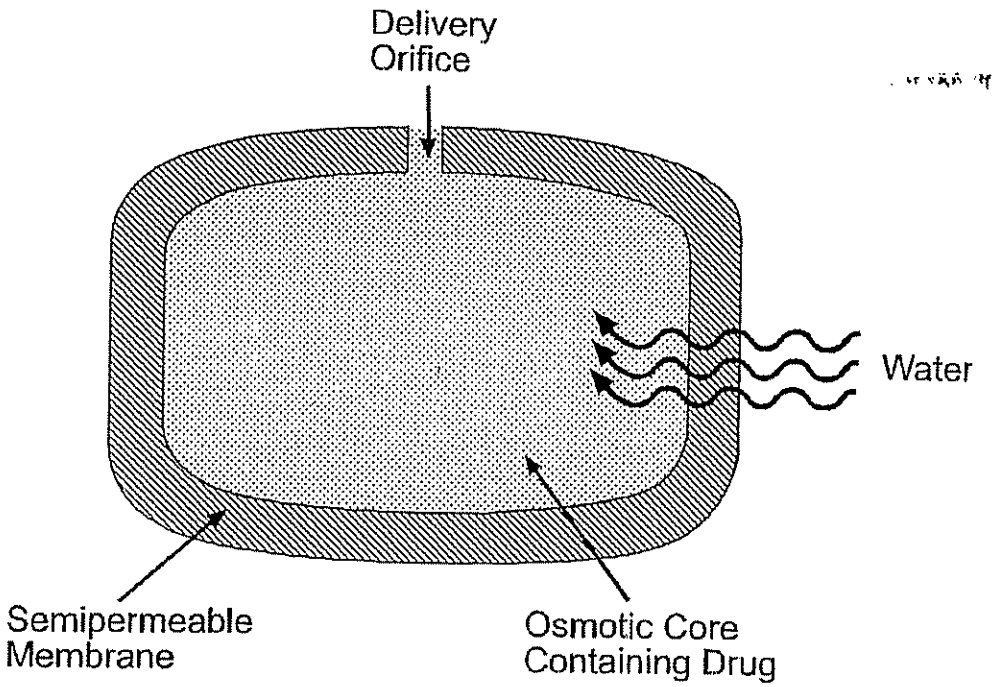

Figure 1 Schematic of elementary osmotic pump (EOP). (Courtesy ALZA Corporation.)

delivered from the system is dependent on the osmotic pressure of the formulation (π_s) as shown in Eq. (4). A schematic of an elementary pump is shown in Fig. 1 (16,17).

$$\frac{dm}{dt} = \frac{A}{h} k\pi_s S \tag{4}$$

where A is the membrane area, k is the membrane permeability, and h is the membrane thickness.

More recently, ALZA Corporation has developed several other controlled release technology platforms based on the original concept of osmosis across a semipermeable membrane. OROS Push-Pull technology has proven to be very useful for delivering compounds of very high or very low solubility such as oxybutynin chloride and nifedipine (18), respectively. OROS Push-Pull technology is capable of zero-order drug delivery for 24 h. As shown in Fig. 2, the system is made of two compartments that are compressed into a bilayer core. The top layer contains the drug and the lower layer contains an osmotic polymeric driving agent. The bilayer tablet is coated with a semipermeable membrane that is drilled on the drug side to allow delivery of the drug formulation through an orifice. During operation, OROS systems imbibe water across the membrane. The push layer expands and drives the drug out of the system in the form of a solution or suspension through the orifice. The release rate of the drug from a push–pull system can be estimated by Eq. 5:

$$\frac{dm}{dt} = \frac{k}{h}\left[A_p(\pi_p - \pi_d) + A\pi_d\right]FC_0 \tag{5}$$

Where F is the initial drug fraction in the drug compartment, C_0 is the solid concentration of the suspension dispensed from the system, A_p is the area of the push layer, A is the total area

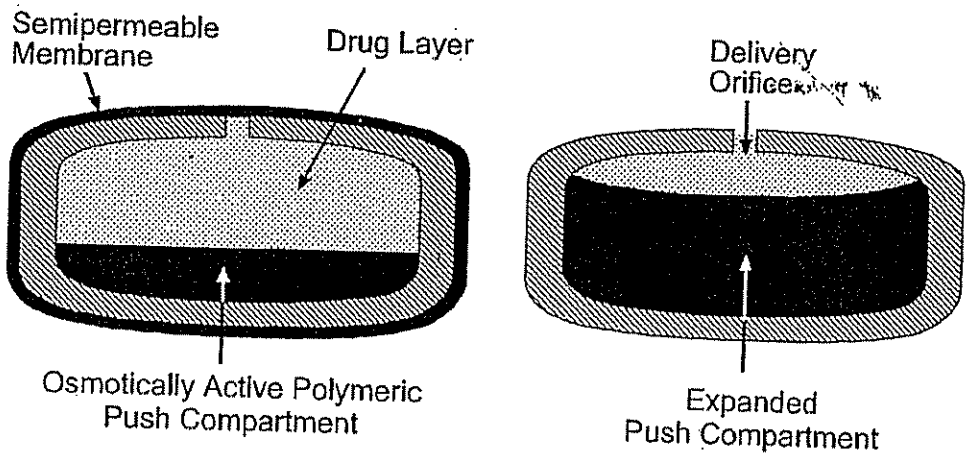

Figure 2 Schematic of OROS "Push–Pull" System (Courtesy ALZA Corporation.) (a) Represents the pump before operation. (b) Represents the pump during operation.

of the system, π_d is the osmotic pressure of the drug compartment, and π_p is the osmotic pressure of the push layer.

Typically, a push–pull system can deliver drug at a constant rate for 80% or more of its theoretical content. OROS systems can maintain zero-order delivery for 24 h. OROS Push–Pull technology has been applied to several commercial products, including oxybutynin chloride (Ditropan XL®), nifedipine (Procardia XL®), and isradipine (Dynacirc CR®). A typical release-rate profile for Ditropan XL® developed by Alza Corporation demonstrates a constant zero-order drug delivery (Fig. 3). The OROS technology has also been customized to suit the needs of a particular drug therapy. A classic example of such an application is OROS verapamil HCl (Covera HS®) for the treatment of hypertension and angina pectoris. The once-a-day system is programmed to provide a delayed onset of drug release after 4–5 h administration. The peak concentration (C_{max}) coincides with early morning hours (when the probability of a stroke is maximum), followed by a constant zero-order delivery.

4. *Ion Exchange Resins*

The idea of using ion exchange resins for controlled drug delivery was adapted from analytical and protein chemistry. Resins are water-insoluble materials containing anionic groups such as amino or quaternary ammonium groups, cationic groups such as carboxylic groups, or sulfonic groups in repeating positions on the resin chain. A drug–resin complex is formed by prolonged exposure of drug to the resin.

Theoretically, this controlled delivery approach is relatively immune to the conditions of the GI tract because an ionic environment is required to displace the drug from the resin. Biphetamine®, a capsule containing equal quantities of amphetamine and dextroamphetamine complexed to a sulfonic acid cation exchange resin, has been used as an antiobesity drug and for behavior control in children (20). Nicorette® is a widely used product based on ion exchange technology as an adjunct to smoking cessation programs. It contains nicotine absorbed to a carboxylic acid ion exchange resin (nicotine polacrilex) in a flavored chewing gum (21). Delsym® (dextromethorphan, Pennwalt), a 12-h cough medication taken as a liquid suspension, is another example of this type of dosage form (22). Further improvement of the ion exchange type of delivery system is illustrated by the development of the Pennkinetic® system (Fig. 4).

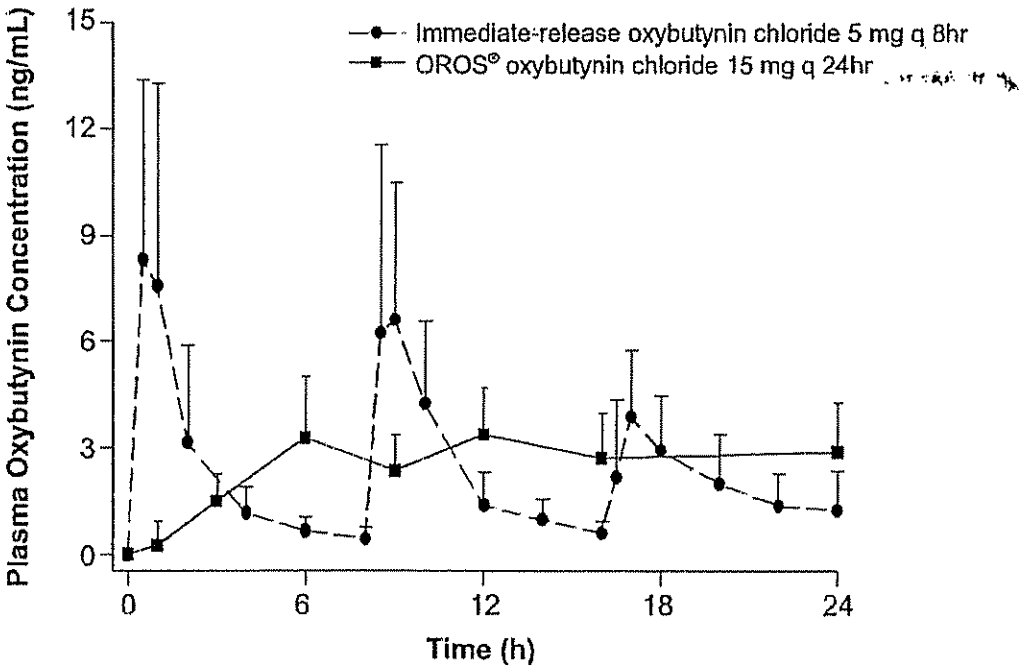

Figure 3 Comparison of mean plasma concentration of immediate release oxybutynin chloride (5 mg, administered every 8 h) with once-a-day OROS oxybutynin chloride (15 mg, administered once daily) after 1 day of administration.

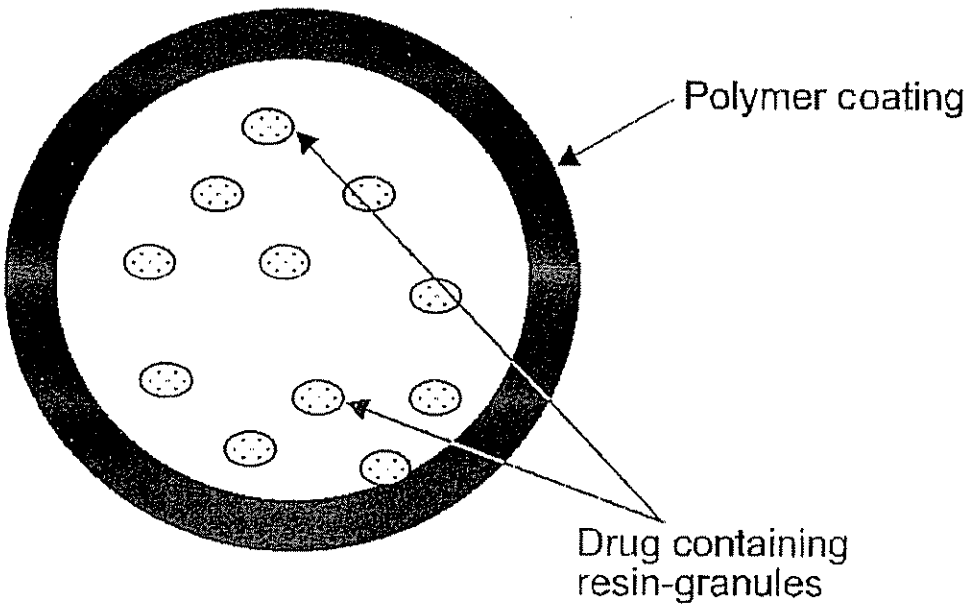

Figure 4 Polymer-coated drug-resin design.

In this system, drug containing resin granules is first treated with a polymer such as polyethylene glycol 4000 to retard the rate of swelling in water, and then further coated with a water-permeable polymer such as ethylcellulose to act as rate-limiting barrier to control drug release.

5 Gastroretentive Systems

Variability in GI transit time is a concern for oral controlled drug delivery systems (23). Drugs with a narrow absorption window in the GI tract are particularly susceptible to variation in both bioavailability and times to achieve peak plasma levels. If successful, gastroretentive controlled release formulations could offer a potential solution to the problem by offering a prolonged gastric residence time (24). A drug that is released from the dosage form in a controlled manner in the stomach will exit the stomach together with gastric fluids and have the whole surface area of the small intestine available for absorption. This type of drug delivery also offers a potential for enhanced drug therapy for local conditions affecting the stomach, e.g., antibiotic administration for *Haemophilus pylori* eradication in the treatment of peptic ulcer.

Researchers in this area have attempted to achieve prolonged gastric retention by several means, including altering the density of the formulations and bioadhesion to the stomach lining. Several strategies have been employed to make the dosage forms float in the stomach. Hydrodynamically balanced system (HBS) was the first formulation that used the floating property of a device with density lower than water (25). HBS is a capsule containing drug, gel-forming hydrophilic polymers (e.g., hydroxypropylcellulose), and some hydrophobic fatty materials (e.g., stearates) (26). In a different approach for gastric retention, ion exchange resin beads are loaded with bicarbonate, which, on contact with media containing hydrochloric acid, release carbon dioxide, causing the resin to float (27). Extension of the floating time is achieved by coating the bicarbonate-coated beads with a semipermeable membrane. Recently, a multiple-unit floating dosage form has been prepared from freeze-dried calcium alginate. In fed subjects, these floating units were retained in the stomach for 5.5–9.0 h (28).

Some hydrogels and superporous hydrogels offer a promising approach to gastric retention. These materials have a swelling ratio of over 1000 (23). They can be made by crosslinking water-soluble polymer chains or by polymerizing hydrophilic monomers in the presence of cross-linking agents. Superporous hydrogels (29) have unique superswelling properties combined with pore sizes in the range of few hundred micrometers to a millimeter. These materials can swell to the equilibrium size in less than 1 min, which is an important requirement for gastric retention devices based on size.

B. Toxicological Considerations

The nonclinical toxicology program required for polymers in oral drug delivery systems depends on a subject's level of exposure to the polymer and to the final product. Exposure should be quantified and should include evaluation of absorption from the GI tract, local distribution, and local tolerance. If the polymer is not a new chemical entity (NCE), a review of the manufacturers' and published scientific literature should be conducted to gather clinical and nonclinical safety information. If the polymer is not absorbed or data indicate that blood levels are acceptable based on historical exposure or existing toxicology data, then it may be sufficient to conduct toxicology studies with the final drug delivery formulation with a written review and justification of the use of the polymer.

If the polymer is an NCE, a series of in vitro and in vivo (animal) genotoxicity studies should be conducted. These mutagenicity and clastogenicity studies determine if the polymer harms the cell's DNA. If the assays reveal a genotoxic result in multiple assays, development of

the polymer should be halted. If no genotoxic activity is present, the next step is to quantify exposure. Is the polymer absorbed from the GI tract? If the polymer is absorbed, a full toxicology program consisting of acute, chronic, reproduction, and carcinogenicity testing is likely to be required. If the polymer is not absorbed, studies up to 6 months long may be required with an evaluation of any proliferative changes. If proliferative changes occur, a carcinogenicity study might be indicated. Whether the polymer is absorbed or not, additional toxicology studies need to be conducted with the final formulation at multiple doses.

C. Functions of Polymers in Oral Controlled Release

For the most part, oral controlled release systems utilize principles such as diffusion, dissolution, and permeation for achieving a constant rate of drug delivery. Polymers are uniquely suited as materials of construction for oral delivery systems. They offer a wide range of properties such as diffusivity, permeability, and solubility that are important to achieving controlled delivery. They can be processed relatively easily into tablets and membranes by a variety of methods. Active ingredients and property modifiers can be incorporated either by physical or chemical means. In reservoir-type devices, polymers are ideal materials to form a membrane around the tablet or granule. These membranes are strong enough to maintain their integrity during normal handling and operation of these systems. Drugs can be dispersed or dissolved into polymers to manufacture matrix-type oral dosage forms. Ion exchange resins are types of polymers to which the drug substances are attached chemically. In general, polymers have little or no toxicity. Superporous hydrogel systems offer excellent ability to swell at a very fast rate, making them potential candidates for gastroretentive devices.

1. Polymer Properties That Affect the Release of Active Substances

A good understanding of polymer properties such as diffusion, solubility, and structural considerations is important in the selection of materials to be used as system components to regulate the fluxes of active ingredients. This section reviews some of these important properties affecting drug permeation.

The flux of a species migrating through a polymeric film is given by Eq. 6:

$$\text{Flux} = \frac{\text{area}}{\text{length}} \times (\text{permeability}) \times (\text{concentration difference}) \tag{6}$$

Area is the surface through which a species is diffusing, and length is the film thickness. Permeability is given by the product of partition coefficient and diffusivity (30).

a. Diffusivity. Diffusivity is the component of permeability that accounts for the geometrical constraints encountered by the diffusing species in weaving across the polymeric film. Consequently, diffusivity increases as the free volume of the polymer increases relative to the dimensions of the diffusing species. Jacobs and Mason (31) have listed various factors that affect the diffusivity of a molecule in a polymeric medium as shown below:

Increases in factor	Effect on diffusivity
Interchain forces	−
Segmental mobility	+
Permeant molecular weight	−
Polymer crystallinity	−
Plasticizer	+
Copolymerization	+

Increases in factor	Effect on diffusivity
Temperature	+
Glass transition	−

b. Solubility Parameter. The active ingredient is either suspended or dissolved in a polymeric matrix in monolithic controlled release systems. Polymers are dissolved in a solvent and coated onto tablets and granules. In reservoir-type systems, for both monolithic and reservoir-type systems, the addition of a second component, such as a drug or solvent, to a polymer can change the strength of polymer intermolecular forces and therefore the physical properties of the polymer. The strength of the intermolecular forces of a polymer is measured by its cohesive energy density (CED). The solubility parameter of a polymer also describes intermolecular forces. The relationship between the solubility parameter, δ, and CED is shown in Eq. 7:

$$\delta = (\text{CED})^{0.5} \tag{7}$$

The solubility parameters for many polymers are documented elsewhere (32). The choice of an ideal solvent to dissolve a polymer for any further processing can be made by comparing the solubility parameters of both polymer and solvent. For example, solvents and polymers with similar solubility parameters will most likely be compatible and soluble in each other. A polymer will precipitate from a solvent with a significantly different solubility parameter.

c. Structural Considerations. The structure of the polymer used in the drug delivery system is a very important parameter determining the mechanism of drug release. The diffusivity of a drug molecule dispersed in a hydrophobic polymer is dependent on the porous structure of the polymer (33,34). The solute diffuses through the solvent-filled pores. As the porosity increases, the release rate of the drug increases. For instance, in macroporous polymers, it is necessary to correct the diffusion coefficient for the porosity, tortuosity, and partition coefficient. For microporous polymers, additional steric hindrance and frictional resistance of the pores also need to be included. For nonporous polymeric networks, both solute molecule and structure of the polymeric network become important in determining the diffusion coefficient. The polymer structure–related factors affecting diffusivity include the degree of crystallinity, the size of the crystallites, the degree of swelling, the molecular weight between crosslinks, and the state of the polymer (whether glassy or rubbery) (35).

Many controlled release tablets and granules utilize hydrophilic polymers for retarding drug release. The mechanism of drug release is dependent on the swelling and dissolution process. An example of such a release mechanism could be demonstrated using tablets manufactured by dispersing drug in hydroxypropyl and hydroxymethylcellulose matrix. In this case, the early part of the release process is marked by swelling due to conversion of the polymer from a glassy to a rubbery state due to water penetration. Subsequently, when the water concentration at the polymer surface exceeds a critical concentration of macromolecular disentanglement, the true dissolution process occurs. Diffusivity through a swollen polymer is much higher than through nonswollen polymers and in fact approach diffusion coefficients in solution.

A detailed listing of polymers used in controlled release oral dosage forms is given in Table 1.

D. Fabrication Techniques

Oral controlled release forms most commonly involve either dispersing the drug into a polymeric matrix, or encapsulating the drug containing core or granules with a rate-controlling membrane. This section describes the most common unit operations involved in the manufacture of oral controlled release products.

Table 1 Polymers Used in Oral Controlled Release Technologies

Method of achieving controlled release	Polymer used	Examples of dosage forms
Matrix or Embedding		
(a) Hydrophillic Carriers	Methyl Cellulose	Multilayer tablets with slow releasing cores
	Sodium Carboxymethylcellulose [38]	Compression-coated tablets
	Carboxymethylcellulose	
	Hydroxypropylmethylcellulose [36,37]	
	Hydroxylethylcellulose	
	Methacrylate Hydrogels [39]	
	Polyethylene Glycols	
	Galactose Mannate	
	Sodium Alginate	
	Polyacrylic acid	
(b) Hydrophobic Carriers		
(i) Soluble Carrier (digestible base)	Glycerides	
	Waxes	
	Fatty Alcohols	
	Fatty Acids	
(ii) Insoluble Carrier (nondigestible base)	Polyethylene	Matrix tablets
	Polyvinyl chloride	
	Polyvinyl acetate	
	Waxes [40]	
	Calcium Sulfate	
Reservoir Type		
(a) Coating with insoluble membrane	Ethyl Cellulose [36, 37]	Granules, pellets, tablets
Osmotic Systems	Vapor permeable walls [41]	Vapor permeable capsules
	- Tenite 808A polyethylene	Vapor permeable tablets
	- Kynar 460 polyvinylidene fluoride	Single and bilayer tablets
	Hydroxypropyl methyl cellulose	
	Hydropropyl cellulose	
	Sodium carboxymethyl cellulose	
	Ethyl cellulose	
Ion-exchange Resins	Dowex® 50, 1, 2 [19]	Controlled release capsules
	Amberlite® IR 120, 400, 4B [19]	Chewable tablets
	Amberlite® IRC 50 [19]	Chewable gums
	With polystyrene-based polymeric backbone	Liquid suspension
Gastric Retention Systems	Hydroxypropyl methylcellulose [24]	Compressed tablets
	Agar, Carrageenans, Alginic acid [24]	Gelatin Capsules
	Oils, porous calcium silicate [24]	
	Superporous hydrogels [29]	
	Ion-exchange resin beads coated with bicarbonate [27,29]	
	Ethyl cellulose for coatings	

1. Wet Granulation

Drug is uniformly dispersed into a polymeric matrix using traditional high-shear granulation (HSG) or fluidized-bed granulation (FBG) techniques. In an HSG technique, an aqueous or a hydroalcoholic binder solution, such as 5% polyvinylpyrrolidone in water, is sprayed onto a polymeric powder bed, such as 85% hydroxypropylmethylcellulose containing the drug. The powder bed is subjected to a very high shear rate to obtain granules incorporating a uniform mixture of drug, binder, and the polymeric excipient. The wet granules could be dried either in a traditional tray dryer, fluidized-bed dryer, or microwave dryer. In an FBG technique, a powder bed consisting of drug, polymer, and other excipients is fluidized in an expansion chamber. The binder solution is sprayed through a nozzle from the top or bottom of the bed depending on the equipment design. The droplet size and bed humidity are the two most important process parameters, which control the granule size and other mechanical properties. The agglomerated mixture can be dried in the same equipment.

2. Spray Drying

Spray drying has been used to produce microencapsulated and matrix formulations of several drug substances including theophylline, acetaminophen, and sulfaethylthiazole. It involves three basic steps. First, a liquid feed is atomized into fine droplets. Second, these fine droplets are mixed with heated gas stream, allowing the liquid to evaporate and leave dried solids. Finally, the dried powder is separated from the gas stream and collected. The final product usually has the same size and shape as the atomized droplet.

3. Spray Congealing

This process consists of suspending the drug particles in a low-melting polymer or wax and pumping the resultant slurry through an atomizer into a spray dryer in which cold air is circulated. The slurry droplets congeal on coming in contact with the air and are collected in the same manner as the spray-dried product. The spray congealing process requires a much higher ratio of coating agent to active material than does spray drying because only the molten coating agent constitutes the liquid phase.

Encapsulation of drug-containing cores and granules in the manufacture of reservoir-type oral controlled released product can be accomplished by the following coating methods:

4 Pan Coating

Pan coaters are one of the earliest types of equipment to be used for encapsulating a drug-containing tablet core. Pan coating involves spraying an atomized coating solution through nozzles on a moving bed of tablets. The distribution of the coating is accomplished by movement of the tablets perpendicular to the application of the coating solution. Drying of the coating solution from the tablet bed is accomplished by directing heated airflow from the front to the back of the partially or fully perforated pan. The popular models include the Hi-Coater from Vector Corporation and the Glatt coater from Glatt Air Techniques Inc.

5 Air Suspension Coating

Granules and pellets are often coated in an air suspension process. Sometimes this technology is also used to apply release-controlling membranes around tablets. Fluidization of tablets or granules is achieved in a columnar chamber with upward flow of drying air. The airflow is controlled so that more air enters the center of the column, causing the tablets to rise in the center. The movement of the tablets is upward toward the center of the chamber. They then fall toward the

chamber wall and move downward to reenter the air stream at the bottom of the chamber. Because tablets and granules hit against the chamber wall during coating, friable tablets are prone to chipping. The drying efficiency of the air suspension coaters is very good. Constant motion of the tablets and granules in the fluidized bed, along with efficient drying, prevents any twinning of tablets or particle agglomeration. Coating solution is applied continuously from a spray nozzle located either at the bottom of the chamber, as in the Wurster process, or atop the cascading tablet bed by nozzles located in the upper region of the chamber. Several models available on the market offer fully automated process capability. Coating uniformity is excellent.

6. Compression Coating

Rate-controlling polymer in the dry powder state can be compressed around the drug-containing core using a special tablet press. This process eliminates the use of any solvents from the manufacturing process. Most often the core tablets containing the drug are prepared prior to the compression coating step. During the compression coating operation, a lower layer of rate-controlling membrane is dosed at the bottom. The drug-containing core is guided to the center of the die followed by another layer of the polymer. Finally, the die contents are compressed under rolls to achieve a hard tablet encapsulated in a rate-controlling polymer. Geomatrix technology uses compression coating to lay a barrier coating of ethylcellulose on a hydrophilic core made of hydroxypropylmethylcellulose to achieve a near-zero-order release rate (36).

E. Future Research

Advances in the design of oral drug delivery systems can be realized by a better understanding of the biology of the GI tract and drug absorption process. So far polymers have contributed immensely to the development of technologies for delivering drug over extended periods. The present state of the art restricts the duration of delivery of oral CR forms to about 24 h. More research effort is needed to retain the dosage forms in the stomach to achieve prolonged as well as higher absorption from the upper GI tract. For instance, new polymers could be designed not only with an extremely rapid onset of swelling, but also with a higher extent of swelling, resulting in prolonged gastric retention. In addition, peptides and proteins are evolving as an important class of therapeutic agents in drug therapy, and absorption of these unstable substances from oral medications is challenging. Polymers could be designed to safely carry these moieties through the GI tract without presystemic clearance, resulting in substantially higher bioavailability.

III. TRANSDERMAL DRUG DELIVERY SYSTEMS

Transdermal systems are currently enjoying widespread consumer acceptance of both prescription and over-the-counter (OTC) products. To many users, the technology is an extension of the "bandage" concept, and therefore relatively noninvasive and easy to use. To a large extent, materials found acceptable for bandages were the starting points for transdermal delivery systems.

A. Designs

There are two predominant designs in transdermal systems: membrane-controlled systems and matrix systems. A brief discussion of the features of each, based mostly on a review article (42), is given below

1. Membrane-Controlled Systems

This type of design essentially consists of three major components: the drug reservoir (often a liquid-containing "form-fill-seal," or FFS, type), the rate-controlling membrane (RCM), and the adhesive. The drug permeates the membrane and the adhesive to reach the skin. Typically, the drug reservoir contains a solution of the drug and liquid excipients. One common excipient used is an enhancer, which also permeates the layers to the skin, where it exerts its enhancing effects by modulating the skin permeability in some fashion. (A variation of this design is the "multi-laminate" RCM design, whereby the drug reservoir is made of solid polymer, with drug dispersed/ dissolved in it; an example is Transderm-Scop.®) In the matrix-type design, the adhesive performs the roles of drug reservoir and adhesive, and to some extent, the role of the rate-controlling membrane as well (See Fig. 5 for schematics of the two systems.)

The major material components of membrane-controlled systems are as follows:

1. The membrane
2. The adhesive
3. The backing, which is also the FFS material

2. Matrix Systems

In this design, the role of the drug reservoir is performed by the adhesive. The drug and excipients are formulated into the adhesive, typically into adhesive solution, and the solvent evaporated to yield the matrix film. The matrix-adhesive film is then laminated to a backing film. Thus, the major components in a matrix design are as follows:

1. The adhesive
2. The backing

The chief advantage of a matrix system is that the entire system can be made thin and elegant, as well as very comfortable to wear. In principle, it is much easier to make an extended wear system (>3 days) using a matrix design than using a membrane-controlled design, as the bulkiness of the FFS type of RCM systems is usually detrimental to comfortable wear. On the other hand, stability issues are more likely to occur in the case of matrix systems, as the drug

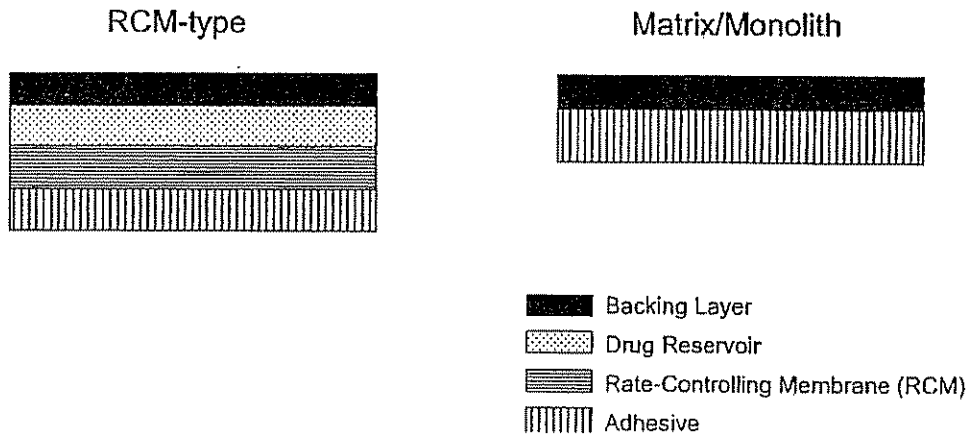

Figure 5 Schematic of membrane-controlled and matrix types of transdermal design.

and excipient may undergo phase changes (e.g., dissolved drug may crystallize or dispersed drug may agglomerate). Both of these causes of instability could adversely affect adhesive properties.

B. Toxicological Considerations

Polymers used in transdermal drug delivery systems may not penetrate the skin themselves, but there may be components of the polymer that migrate. The polymer and extracts should be biocompatible since they are in contact with components that do penetrate the skin. The tests listed in ISO/ANSI/AAMI Standard 10993, Biological Evaluation of Medical Devices are intended to provide testing strategies for medical devices. There are similar guidelines in the U.S. Pharmacopoeia 23 for plastics used as drug containers. These tests may also be used to test biocompatibility of polymers used in transdermal drug delivery systems. Extracts may also be tested for the potential to cause topical sensitization. Preparation of polymer extracts is defined by the guidelines, but the choice of conditions should come close to the conditions of manufacture of the drug delivery system. Extracts are evaluated in in vitro cytotoxicity tests and in in vivo irritation, intracutaneous injection, systemic injection, and implantation studies. A sample of the polymer may also be evaluated in these in vivo tests. The final transdermal drug delivery system must also be evaluated in standard nonclincal toxicology studies to evaluate the safety of the system. These studies should detect adverse effects of the system as well as any adverse effects of polymer extracts that are not detected in the previous tests. Study duration will depend on whether the active drug is an NCE and on its duration of use.

C. Delivery Profiles/Performance

The strength of the RCM-based design is constancy of drug delivery to the skin. In kinetic terms, the RCM design affords the possibility of zero-order release, i.e., the rate of drug delivery to the skin is constant with time. On the other hand, the matrix design can yield only a nonconstant rate of drug delivery to the skin. Typically, this rate decreases with time such that the amount delivered is proportional to the square root of time rather than to time. In either case, the likelihood of constancy of delivery of drug to the bloodstream is determined by the flux through skin relative to flux through the system alone. In limiting cases, the following is true:

When drug flux through skin is very low (< approximately 10% of flux through device), the skin is termed rate controlling: in this instance, both types of designs can yield zero-order delivery to the bloodstream.

When drug flux through skin is high (> approximately three times the rate through device), then only the RCM design can yield zero-order kinetics for drug delivery to the bloodstream

When dealing with potent drugs or with drugs that have a narrow therapeutic window, the RCM design yields a greater margin of safety, but the level of safety is contingent on the level of control attained by the device as opposed to the skin. In addition, RCM systems also tend to demonstrate a lesser degree of patient-to-patient variability, for the same reasons outlined above. Matrix systems, on the other hand, are preferred for drugs that have very low skin flux, as they can achieve higher release rates. In addition, as mentioned above, matrix systems tend to be more appealing to the patient and may lead to greater acceptance.

Table 2 shows the commercial transdermal systems by type of design, and lists the materials used in each system

Table 2 Family of Commercial Transdermal Systems

Product name	Innovator	Marketer	Active ingredient	Systems area(s)	Delivery rate(s)	Rated duration	Enhancer	Type
Alora®	TheraTech	P&G Pharm.*	17β-estradiol	18, 27, 36 cm^2	0.05, 0.075, 0.1 mg/d	4 days	sorbitan monoleate	Adhesive matrix
Climara®	3M Pharm.	BerlexLabs	17β-estradiol	12.5 & 25 cm^2	0.05 & 0.1 mg/d	7 days	fatty acid esters	Adhesive matrix
Deponit®	Lohman	Pharma						
	Neuwied FRG	Schwarz	Nitroglycerin	16 & 32 cm^2	0.2 & 0.4 mg/h	12–14 hr	"a plasticizer"	Adhesive matrix
FemPatch®	Cygnus	ParkeDavis	17β-estradiol	30 cm^2	0.025 mg/d	7 days	propylene glycol monolaurate	Adhesive matrix
Habitrol®	Novartis	Novartis	Nicotine	10, 20, 30 cm^2	7, 14, 21 mg/d	24 hrs	none	Pad in adh. matrix
Minitran®	3M Pharm.	3M Pharm.	Nitroglycerin	20 cm^2	0.6 mg/h	12–14 hr	fatty acid esters	Adhesive matrix
Nitrodur®	Key Pharm.	Key Pharm.	Nitroglycerin	10, 20, 30, 40 cm^2	0.2,0.3,0.4,0.6,0.8 mg/h	12–14 hr	none	Adhesive matrix
Testoderm® with adhesive	Alza	Alza	Testosterone, USP	60 cm^2	6 mg/d	24 hrs	none	Matrix, striped adh
		Ciba, RPR-Novo					oleic acid, propylene	
Menorest®, Vivelle®	Noven	Nordisk**	17β-estradiol	11 & 29 cm^2	4 Rates, 25–100 ug/d	3–4 days	glycol	Adhesive matrix
Nicotrol®	Cygnus	McNeil	Nicotine	30 cm^2	15 mg/16 h (1 day)	16 hrs	none	Adhesive matrix
		SmithKline					ethanol, glyceryl mono	
Androderm®	TheraTech	Beecham	Testosterone, USP	37 & 44 cm^2	2.5 & 5 mg/d	24 hrs	oleate, methyl laureate, glycerin	FFS***, peripheral adhesive
Prostep®	Elan	Elan	Nicotine	3.5 & 7 cm^2	11 or 22 mg/d	24 hrs	none	Matrix, peripheral adhesive
Nitrodisc®	Searle	Searle	Nitroglycerin	8, 12, 16 cm^2	0.2, 0.3, 0.4 mg/h	24 hrs	polyethylene glycol, isopropyl palmitate	Matrix, peripheral adhesive
		Boehringer						
Catapres TTS®	Alza	Ingelheim	Clonidine	3.5, 7 & 10.5 cm^2	0.1, 0.2, 0.3 mg/d	7 days	none	rate-control memb.
Duragesic®	Alza	Janssen	Fentanyl	10,20,30,40 cm^2	25,50,75,100 ug/d	3 days	ethanol	rate-control memb.
Estraderm®	Alza	CibaGeneva	17β-estradiol	10 & 20 cm^2	0.05 & 0.1 mg/d	3 days	ethanol	rate-control memb.
		SmithKline						
Nicoderm®CQ	Alza	Beecham	Nicotine	7, 15 & 22 cm^2	7, 14 & 21 mg/d	24 hrs	none	rate-control memb.
Transderm-Nitro®	Alza	CibaGeneva	Nitroglycerin	5,10,20, & 30 cm^2	0., 0.2, 0.4 & 0.6 mg/h	12–14 hrs	none	rate-control memb.
Transderm Scop®	Alza	Novartis	Scopolamine	2.5 cm^2	0.5 mg/3 d	3 days	none	rate-control memb.

*Proctor and Gamble Pharmaceutical; **RPR = Rhone-Poulenc Rohrer; ***FFS = Form-fill-seal.

D. Polymer Requirements

For the sake of convenience, this discussion of materials used is divided in terms of the design type.

1. RCM-Based Systems

As mentioned above, the chief components of RCM a designs are the FFS material, the rate-controlling membrane itself, and the adhesive.

a. FFS materials. The requirements for the FFS material is that it should be as follows:

1. Thermoformable
2. Sealable to the membrane material
3. Occlusive (low moisture–vapor transmission rate; MVTR)
4. Impermeable to volatile excipients of the formulation
5. Nonabsorptive for the drug

Materials that meet these requirements include polyester (PET)/heat-seal layer laminates, or PET/metal/heat-seal layer laminates. Available trade names include Scotchpak® from 3M Company and Mediflex® from Bertek, Inc., in a range of thicknesses. These two vendors are also willing to custom-fabricate laminates. The PET layer confers the impermeability and low-MVTR attributes to the device backing, while the occlusivity is attained by the combination of material and thickness. Thermoformability is not a requirement when the drug formulation has high viscosity and can be contained relatively easily. However, when the drug formulation is predominantly liquid-like, the material must be capable of being formed (preferably by thermal means) into a cavity. An example of such material includes is polypropylene.

Examples of products that use the RCM design include Estraderm®, Transderm-Nitro®, and Testoderm TTS®; the first two are marketed by Novartis, while ALZA Corporation markets Testoderm TTS.

b. Membranes. The RCM is the critical component of the membrane design. It must satisfy the following criteria:

1. A diffusion coefficient for the drug under consideration that ranges from about 10^{-7} to 10^{-9}
2. Capable of being fabricated into a film of thickness from 1 to 5 mils
3. Low solubility for the drug and its excipients
4. Should be capable of being laminated to the FFS material on one side and the adhesive on the other
5. Should soften well above shipping temperatures
6. Modulus should be about 1000 to 1 MM Pa

Both homopolymer and copolymer films can be found that satisfy the above criteria. The 3M Company has developed the CoTran® series of membranes based on polyethylene and ethylene vinyl acetate (EVA, 9% vinyl acetate). The polyethylene films can be nonporous or microporous, whereas EVA is an extruded film. Also noteworthy are the Celgard® membranes from Hoechst-Celanese; these are also microporous films based on polyethylene and polypropylene. These are produced by a patented stretching process that introduces pores into the film. Celgard films are available with both hydrophobic and hydrophilic surfaces.

The copolymer EVA has long been the polymer of choice in this category. This is primarily because the vinyl acetate content can be varied to tune its permeability to meet the requirements of the drug under consideration. In general, the variables available for manipulation of the permeability of the material are the vinyl acetate content, thickness, crystallinity of the

ethylene components, and domain structure of the fabricated film. The following table lists the various grades of EVA available and measured diffusion coefficients for selected drugs (43):

	9% EVA		18% EVA		40% EVA	
Percent EVA	K.I	$D \times 10^9$	K.I	$D \times 10^9$	K.I	$D \times 10^9$
19-nor-Progesterone	4.9	4	18	3	105	5
Testosterone	4.0	4			88	5
Estriol	0.0048	4	0.025	3		

K.I = normalized permeability coefficient, $\mu g/cm.s$
D = coefficient of diffusion, cm^2/s

Note that in the above examples, the diffusion coefficient remains unchanged for the different EVAs, whereas the permeability changes by factors of 10–25 This is explained by postulating that the diffusion coefficient is dependent on factors such as pore size, which in turn is determined by the amount of crystallinity in the material and how the crystallites are distributed (morphology). In this instance, as long as the average pore size is above a threshold value, the diffusion coefficient is unchanged in going from 9% to 40% EVA. The permeability, which is also dependent on the partition coefficient, is expected to change as the EVA content changes. This is borne out experimentally.

c. Adhesives. In membrane-controlled systems, the adhesive must exhibit permeability for the drug and the enhancer that is defined by the delivery profile of the drug under consideration At any time it is likely that the adhesive has measurable amounts of drug and enhancer dissolved in it to their solubility limits, as the typical process is one of partitioning followed by diffusion. If the solubility of either component is low, then the permeation process does not appreciably affect the adhesive. If it is substantial (>3% by weight), then the following effects may be anticipated: liquid excipients (including drug) will "plasticize" the adhesive to some degree; if the period of wear is long (>24 h), this could lead to unsightly residue and oozing on skin. The "oozing", in addition to being unsightly, also collects dirt and lint, and occasionally sticks to clothing. If the drug and excipients are solids, the adhesive may increase in cohesive strength and lose some of its adhesive characteristics, particularly tack. Thus, the optimum choice of adhesive for the RCM design depends on drug and excipient solubility.

All of the commonly used adhesives are derived from the pressure-sensitive adhesive (PSA) industry. Used in such products as Post-It® notes, and also in automotive decals, office labels, and other applications, the same basic adhesives have been requalified for use in the transdermal field. Requalification typically involves animal and human toxicology testing, as well as incorporation of the material into a Drug Master File (DMF).

Classes of PSAs available include:

1. Polyacrylate are copolymers of acrylates with vinyl acetate, alkyl acrylate, acrylic acid, or other functional monomers and are by far the most commonly used. Major suppliers include National Starch & Chemical Co., Morton-Thiokol, the Solutia division of Monsanto Chemical Co., and Adhesives Research. The 3M Company formulates its own acrylic adhesives for incorporation into 3M transdermal products (predominantly matrix-type constructions).
2. Silicones are also used in many transdermal systems, due primarily to their excellent adhesion characteristics and a perceived hypoallergenic nature However, these are

made by two suppliers, Dow-Corning and NuSil Technology, and continue to be expensive.

3. Polyisobutylenes (PIBs), in mixtures with polybutene and tackifiers, are also heavily used. Suppliers, including Adhesives Research, Inc. ALZA Corporation, and Cygnus, Inc., have their own versions of PIB adhesives in some of their transdermal systems.
4. Natural rubber–and synthetic rubber–based adhesives are also available from National Starch Co. However, some of these suffer from complexity in their composition, while the natural rubber–based adhesives tend to be also somewhat more irritating than their counterparts.

2. Matrix Designs

The major components of this type of design are the backing material and the adhesive.

a. **Backing Materials.** The backing material must satisfy the following criteria:

1. Occlusive (low MVTR)
2. Impermeable to volatile excipients of the formulation
3. Nonabsorptive for the drug

Since the requirements are less stringent than those for FFS materials, a wider choice is available. Typically, polyesters, e.g., poly(ethylene terephthalate) (PET), polyolefins (HDPE or LDPE), multilayered films (Saranex from Dow Chemical), or elastomers can be used. In fact, it is claimed (44) that the elastomeric backings have more acceptable long-term wear. A sandwich of polyurethane/polyisobutylene/polyurethane has also been claimed (45). The commercial system, Fempatch®, utilizes an elastomeric backing layer. Patents for other elastomeric backings also exist (46).

b. **Adhesives.** Although the same classes of adhesives mentioned above are also used for the matrix systems, other additives have to be formulated into these adhesives. Therefore, the demands made of the adhesive in this design are far more exacting. The adhesive contains all of the drug and any excipients. The drug and excipient could be dissolved or dispersed, depending on the amount needed for the appropriate delivery profile. If the additives need to be dissolved and stay dissolved, then the choice of adhesive is determined solely by solubility characteristics. In the case of dispersed systems, the range of useful adhesives increases, but the effect on properties is different. Dissolved additives tend to decrease moduli and render the adhesive more susceptible to creep/cohesive failure. Dispersed additives tend to reinforce the adhesive, especially if the additive is a solid. Thus, adhesive selection for matrices is more complicated and entails compatibility studies, long-term stability studies of the adhesive, and optimization of the formulation, based on the nature of the additives.

E. Fabrication

For RCM designs, fabrication involves the incorporation of the drug formulation into an FFS construction. This process may involve forming, filling, and sealing, or just filling and sealing, depending on the state of the formulation (paste, viscous liquid, or liquid). Once the formulation is contained, the subsequent steps involve sealing the FFS material to the membrane and the lamination of membrane to adhesive. Sometimes the membrane is made part of the FFS material by a suitable lamination process prior to incorporation of drug formulation.

The major steps in the fabrication process for RCM systems are as follows:

1. Mixing of drug formulation
2. Form, fill, and seal

3. Lamination to adhesive
4. Die-cut, pouch, label, and package

The throughput is mostly dependent on the first of these processes. The FFS operation itself is dependent on formulation viscosity or dispensing speed. Metering pumps are often used for the dispensing process. Typical line speeds are about 30 ft/min.

For matrix designs, fabrication includes the following steps:

1. Mixing of drug formulation with adhesive solution
2. Casting mixture onto backing material or release liner
3. Evaporation of solvent
4. Laminating to backing material
5. Die-cut, pouch, label, and package

The throughput is determined mostly by the casting operation, which involves spreading the adhesive/drug formulation onto a moving web, and then evaporation of the volatile components. The line speed is determined by the nature of the solvent. Typical speeds are about 5–20 ft/min.

F. Issues and Opportunities

The factors limiting the advancement of transdermal technology are not related to polymers. The key factors are the ability to push small molecules through the skin faster and the problems associated with sensitization from certain drug classes. For example, the so-called lag time in transdermal administration (the time required for the drug to reach efficacious blood levels) is still of the order of 2–4 h for most drugs, and this may be unacceptable if immediate relief is desired. In another example, the flux requirements for a given drug are so high that very large patches are needed. In these cases, advancement will occur through the invention/discovery of new enhancers rather than new polymers, although new polymers may be needed to accommodate and deliver the new enhancers at an acceptable rate. Similarly, the issue of sensitization by certain drugs cannot be overcome by the use of new polymers. Coadministration of immune suppressants or modification of drug structure to an immunologically inert form may be required. Such advances will enable the transdermal administration of antihistamines, for example.

IV. IMPLANTABLE DRUG DELIVERY SYSTEMS

For the purposes of this chapter, implantable drug delivery systems are defined as long-term (greater than 30 days) implantable products that are resorbable or removable. The resorbable "implants" are really injectables incorporating lyophilized microspheres and will be discussed further in Section V. The removable version is typically a subcutaneous implant, requiring a minor outpatient procedure for both insertion and removal. The main commercialized product in this category is Norplant®, a contraceptive implant. A limited number of other companies have announced products in various stages of development, the leading candidate being the Duros technology from ALZA Corporation (currently in phase III trials). Medtronic Corporation has two products in the implantable area that allow drug delivery into the intrathecal space (where the spinal fluid circulates). One of these products delivers baclofen for spasticity and the other delivers anesthetics for pain control. Both products utilize Medtronic's SynchroMed® infusion pump, which can be electronically programmed to deliver any type of preset dose. However, this type of product falls outside the scope of this chapter, which will focus on removable implanted passive devices.

A. Designs

The Norplant® product was developed by the International Committee for Contraception Research (ICCR) of Population Council, Inc. It is marketed in the United States as a 5-year implant by Wyeth-Ayerst. The first-generation product consists of a set of five cylindrical pieces that are inserted subdermally using a simple procedure. This particular version of Norplant is a capsule system (labeled case I in Fig. 6) in that crystals of levonorgestrel (LN) are encapsulated by Silastic® polymer. Later designs being tested internationally by the ICCR include a Silastic matrix (case II in Fig. 6), in which micronized LN is dispersed and a covered rod (case III in Fig. 6), which is a membrane-coated matrix. The three designs are depicted schematically in Fig. 6. The three designs yield very different release profiles, partly due to the nature and amount of drug loading, and partly due to design features. The three release profiles (47) are shown schematically in Fig. 7.

As can be seen from the figures, the drug release rate in case I is constant after 450 days (~15 months), whereas case II (matrix) yields a rate that varies as the square root of time, and case III yields a nearly constant rate over time. Although in principle cases I and III (membrane-controlled systems) are expected to yield constant-rate (zero-order) profiles, case I yields an initial nonconstant rate because of the nature of the drug present in the capsules. Levonorgestrel is present as crystals in the capsule, and it has been noted that water permeates slowly into the capsule. At about ~450 days, the drug is virtually suspended in water, and the rate-determining step becomes the dissolution rate of levonorgestrel in water (48). Case II exhibits the classical matrix rate profile, whereas case III yields the classical membrane-controlled rate profile.

Research on optimizing the design in order to achieve constant rates over long periods, as well as to maximize drug loading (so that the size or number of rods can be reduced), continues, with contraception as the main focus.

Using a totally different approach, ALZA Corporation has developed the Duros® implant (see discussion elsewhere in this book) to deliver constant amounts of drug over periods

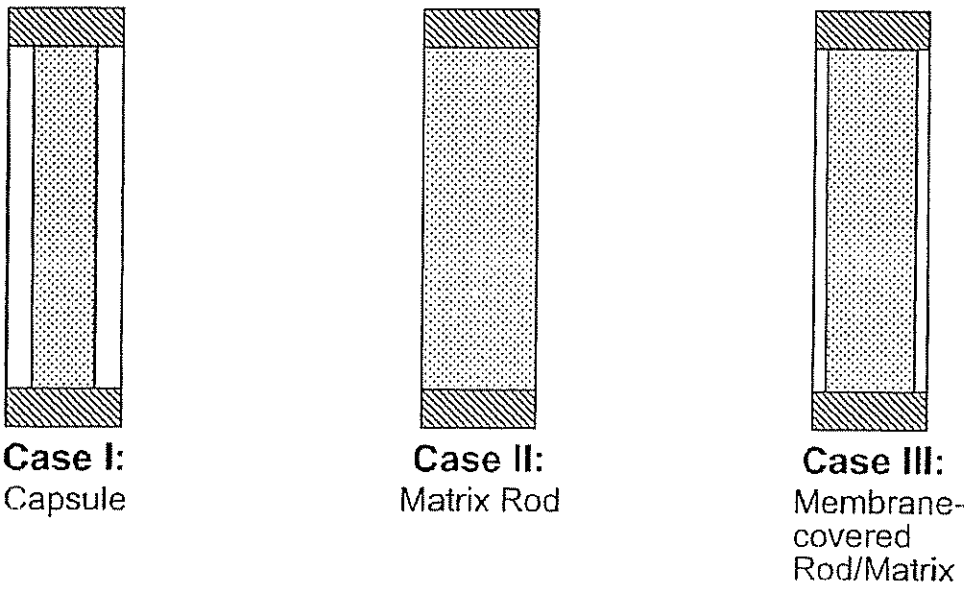

Figure 6 Three types of long-term implant designs

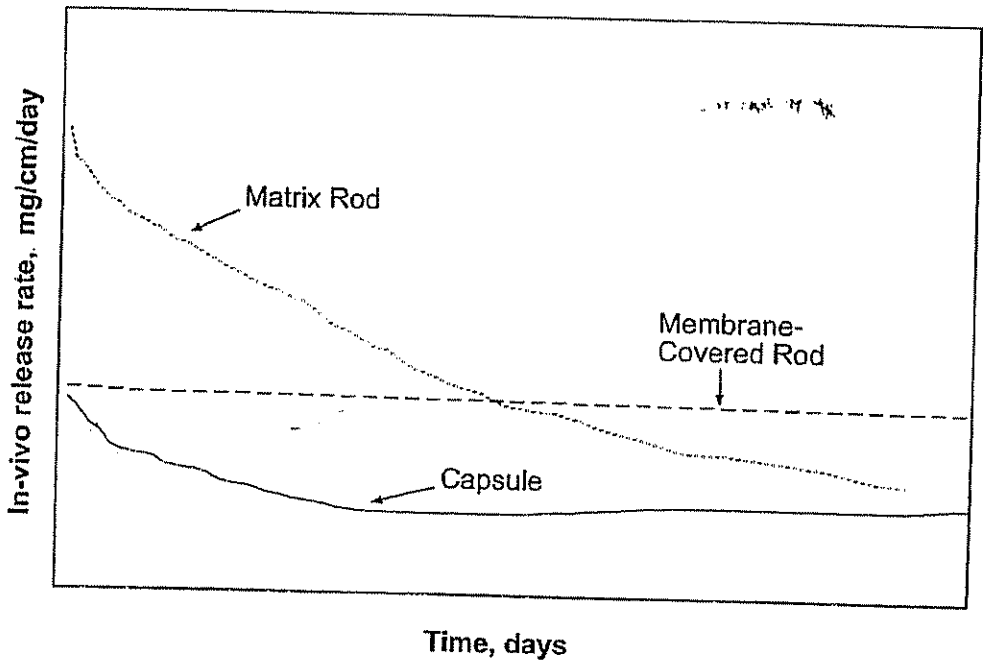

Figure 7 Drug release characteristics of three types of implants.

ranging from 3 to 12 months. The principle used in this design is essentially the same as the one used in the OROS system for oral controlled release. Basically, the osmotic engine draws in water at a constant rate through a semipermeable membrane, and this water causes an increase in hydrostatic pressure inside the device. That pressure pushes the drug out at a constant rate through a small orifice at the end opposite of the membrane. The rate of drug efflux is proportional to the rate of water ingress into the device. The water ingress rate is manipulated by the nature of the membrane material, as well as by its geometry.

Rates of drug release for the Duros are constant over 3–12 months, as shown in the chapter devoted specifically to this delivery system. The constancy of rate is achieved by regulating the rate of water ingress into the osmotic engine, rather than by manipulation of diffusion of drug, as is the case with the Norplant design. In that regard, the choice of the membrane material is the key to performance of the Duros device.

B. Toxicological Considerations

Polymers in implantable drug delivery systems must be toxicologically evaluated as with other drugs or excipients. The nonclinical toxicology program required for polymers in implantable drug delivery systems depends on exposure to the polymer, extracts (including residual monomers, process additives, and degradation products), and the final product. Exposure should be quantified and include evaluation of local distribution and local tolerance.

If the polymer is a structural component of the implant, a determination of leachables of the polymer in the drug vehicle is appropriate. The polymer and extracts should be biocompatible since they are in contact with components that are systemically released. The tests listed in ISO/ANSI/AAMI Standard 10993, Biological Evaluation of Medical Devices are intended to

provide testing strategies for medical devices. There are similar guidelines in the U.S. Pharmacopoeia 23 for plastics used as drug containers. These tests may also be used to test biocompatibility. Extracts may also be tested for the potential to cause topical sensitization. Preparation of polymer extracts is defined by guidelines, but the choice of conditions should come close to the conditions of manufacture of the drug delivery system. Extracts are evaluated by in vitro cytotoxicity tests and in vivo irritation, intracutaneous injection, systemic injection, and implantation studies. A sample of the polymer may also be evaluated in these in vivo tests.

If the polymer is released systemically and not a new chemical entity (NCE), a review of the manufacturers' and published scientific literature should be a conducted to gather clinical and nonclinical safety information. If data indicate that blood levels are acceptable based on historical exposure or existing toxicology data, then conduct of toxicology studies that include the final drug delivery formulation with a written review and justification of the use of the polymer may be all that is necessary.

If the polymer is released systemically and is an NCE, a series of in vitro and in vivo genotoxicity studies should be conducted. These mutagenicity and clastogenicity studies will evaluate if the polymer and/or extract harms the cell's DNA. If the assays reveal a genotoxic result in multiple assays, development of the polymer should be halted. If no genotoxic activity is present, a full toxicology program consisting of acute, chronic, reproduction, and carcinogenicity testing will in all likelihood be required. Additional toxicology studies would necessarily be conducted with the final formulation.

C. Polymer Requirements

In the Norplant-type system, the membrane material has to satisfy the following criteria:

1. Should satisfy the long-term toxicological requirements, as outlined in Section IV.B.
2. Should not promote fibrotic tissue growth upon itself.
3. Should have the appropriate diffusion coefficient for small molecule drugs.
4. Should be capable of being fabricated into cylinders of varying sizes.
5. Should have low solubility for the drug in question
6. Must be flexible enough so as not to be "felt" by the user. Typically, the modulus should be in the elastomer range of about 10^6 dynes/cm^2 or 100,000 Pa.

In actual use, the last of these requirements turns out to be inappropriate. While it is true that flexibility led to user acceptance, removal of the rods after use for prolonged periods in the body (~2 years or more) presented problems, as it became difficult to locate the rods. The ALZA design circumvents this problem by substituting a harder material for the body of the implant, at some cost to user acceptance. For the ALZA design, the two most important materials (outer container material and the rate-controlling membrane plug) must satisfy not only the toxicological and fibrotic growth requirement, but the container material must be rigid, and locatable either by feel or by other techniques, after prolonged use. This material must also have negligible solubility for the drug or the excipients, and negligible diffusion coefficient for the components of the drug formulation. The membrane plug material, on the other hand, must (in addition to the first two requirements above) have the following characteristics:

1. Possess a reproducible and well-defined permeability coefficient for water
2. Be moldable by standard polymer fabrication procedures
3. Retain its shape (under the constraints of the container material) without appreciable swelling in the presence of bodily fluids

In the next section, some of the materials and their characteristics will be explored.

D. Materials of Use

The earliest version of Norplant used six identical cylindrical rods (2.4 mm o.d., 1.57 mm i.d., 30 mm filled length) made of Silastic, a polydimethylsiloxane polymer made by Dow-Corning. The particular one used was Silastic medical-grade elastomer 382. This is a catalyst-cured siloxane elastomer, which for the implant application is also filled with silica. Essentially, thin-walled tubes were fabricated from this material, and sealed at the ends after having been filled with levonorgestrel crystals.

Later versions of Norplant include the rod and the covered rod. The rod is essentially a matrix of drug homogeneously dispersed inside the Silastic elastomer, whereas the covered rod comprises a core rod of PDMS and levonorgestrel, sealed inside thin-walled medical-grade Silastic tubing, using medical-grade Silastic adhesive. Practically all of this work derives from the early work of Folkman and Long (49), which evaluated the diffusion of small molecules through Silastic material. Repeated use of this material has ensured its continuance as an implant material, whereas others have not been subject to enough long-term studies to warrant use as a long-term implant material. In developmental work, however, poly (ϵ-capralactone) has been studied extensively in a development product called Copranor® (50). In the reported study, effective diffusion rates were obtained for levonorgestrel, testosterone, and progesterone. Biodegradable polymers such as esters of poly(lactic acid) and poly(glycolic acid), while acceptable as implant materials, generally exhibit too low a diffusion rate for most drugs of interest. The reason for this is that the PLA-PGA copolymers generally have too high a T_g, whereas both poly(ϵ-capralactone) and silicone elastomers have low, subambient T_g values.

In the Duros system, the outer container is constructed from a titanium alloy. The critical rate-controlling membrane is fabricated from a proprietary polyurethane developed specifically for ALZA Corporation. Early clinical data show little to no fibrotic growth around the implant body or its ends; more details are available elsewhere in this book.

E. Fabrication

The Norplant capsules are fabricated by first extruding tubes of Silastic, then filling with crystals of levonorgestrel, and then subsequently sealing the ends of the tube with silicone medical adhesive. Presumably, diffusion through the thin walls of the tube (approximately 15 mils) is the rate-controlling step, whereas diffusion through the ends (~150 mils) is much slower because of the higher pathlength.

The rods are fabricated by mixing about 25% by weight of steroid with a stannous octoate catalyst and Silastic 382, then pouring into a mold. Typical dimensions of rods are 2.4 mm diameter and 2 or 3 cm length.

Sterilization is carried out using ethylene oxide rather than radiation, since radiation further crosslinks the silicone and leads to a reduction in diffusion rates. Earlier studies had indicated that radiation affects the drug more than the polymer, but later studies have not borne this out. In any case, the preferred method of sterilization is by use of ethylene oxide.

Details of fabrication of the Duros device are given elsewhere in this book.

F. Issues and Opportunities

The use of biomaterials in human implants underwent a significant change in the early 1980s when the first of the silicone breast implant suits hit the courtrooms. Favorable and substantial awards to the plaintiffs resulted in bankruptcy for Dow-Corning. Subsequent lawsuits were directed at the parent companies of Dow-Corning, resulting in Dow Chemical making payments as well. All of this had very adverse consequences for the use of silicone materials

in humans. Several companies, particularly the larger ones such as DuPont, Shell Chemical, and Exxon, made it corporate policy to not allow the use of any of their materials in inside-the-body applications.

In this context, the passage of the recent Biomaterials Access Assurance Act (H.R.872, Public Law 105-230, passed 8/98) is of great significance to biomaterial suppliers. The Act specifically exempts a supplier from liability for harm to a client caused by an implant, provided the supplier is not the implant manufacturer, and provided the supplier has supplied raw materials that meet contractual requirements and specifications. This should open the door for small and big firms to enter or reenter the biomaterials supplier market, but economics may drive the decision more than the perceived exemption from liability. Certainly, if the market is sizable for the polymer in question and/or if manufacturers of the implant are willing to pay a premium for implantable biomaterials, bigger firms will reenter the field. Otherwise the status quo will prevail, with smaller firms supplying materials to the industry. However, in all likelihood, the number of suppliers for any given biomaterial will increase, eventually driving prices down to manageable levels. The onus of testing and proving the safety of the implanted biomaterial will rest squarely on the implant manufacturer in each instance.

V. MICRO- AND NANOPARTICLE DELIVERY

Microparticles and nanoparticles incorporate drug in matrix or encapsulated form, delivered to the body via injection (IM, IV, or subcutaneous), via the oral cavity or via the nose. Control of delivery is typically achieved by one of the following mechanisms:

1. Diffusion through the coating of the capsules (for encapsulated particles)
2. Diffusion through the matrix of the particles
3. Erosion of the coating material
4. Erosion of the matrix material

For nasal and oral delivery, the particles are typically in the 20-μ to 100-μm range, since smaller particles can be inhaled and may make their way to the lung for alveolar delivery. For injectable delivery, to achieve prolonged duration of effect, the particles tend to be in the 50- to 100-μm range. Nanoparticles are classified as having diameters below 1 μm and tend to be used specifically for targeted drug delivery, usually via the injectable route.

The field of micro- and nanoparticles used in drug delivery is so broad an area of research that to list all of the applications and associated polymers is not practicable. It is convenient to subdivide this category as follows:

1. Bioadhesive microparticles
2. Injectable biodegradable depot formulations
3. Nanoparticles

The bioadhesive particles are typically formulated for mucosal delivery; this includes GI, buccal, nasal, and vaginal delivery. Injectable depot formulations invariably use biodegradable polymers, whereas nanoparticles may employ biodegradable and nonbiodegradable polymers. The rationale behind this subclassification is that for prolonged duration of delivery some bioadhesiveness is required of mucosal delivery vehicles, while depot formulations do not have this requirement. Nanoparticles are conceived to be used exclusively in injectable delivery and so are not required to bioadhere.

It is pertinent to make some general observations before proceeding to the specifics of each of these types of microparticulate delivery.

1. No product using bioadhesive particles has found commercial success to date. The products that offer prolonged action in mucosal delivery are nasal sprays, which do not employ bioadhesive microparticles. Therefore, we will survey the research on these particles to date and the materials employed in such formulations.
2. Depot formulations using biodegradable particles have been commercially successful, e.g., Lupron Depot®.
3. Nanoparticulate delivery is in early stages of research.
4. It is fair to say that, except for the case of biodegradable polymer matrices, formulations with microspheres tend not to have sustained or controlled release characteristics. Even in the case of microcpasules, the coating uniformity determines the degree of control over the release characteristics, even though in principle, membrane-coated particles can possess a controlled release profile. Furthermore, there is always a distribution of sizes in any of these preparations, and since surface-to-volume ratio also influences release kinetics, there is bound to be a distribution of rates achievable with any given preparation.

A. Mucosal Delivery: Bioadhesive Materials

In the field of mucosal delivery, the focus has been on two aspects of delivery:

1. Improving duration of action using mucoadhesive particles
2. Improving bioavailability of peptide drugs by enhanced delivery across the mucosa

For improving mucoadhesion, a variety of polymers have been tried with varying degrees of success. Perhaps the most mentioned polymer is a poly(acrylic acid) that is sold under the trade name Carbopol® by B.F. Goodrich. A variety of in vitro studies have claimed superior mucoadhesion for this polymer (51). In particular, the crosslinked poly(acrylic acid) known as polycarbophil has been claimed to have superior mucoadhesive properties. The crosslinking is usually carried out using divinyl glycol; crosslinked resins are available from B.F. Goodrich under the trade name Noveon®. This polymer has found successful use in three commercial products from Columbia Laboratories. These are not strictly microparticulate formulations but involve gels made of mucoadhesive polymer. They are discussed here as examples of commercialized mucoadhesive formulations:

Replens®—a vaginal moisturizer product utilizing polycarbophil in an aqueous gel formulation; duration of action is claimed to be several days

Advantage 24®—a vaginal contraceptive product, also utilizing a polycarbophil aqueous gel but containing a spermicide, nonoxynol 9 (3.5%); and

Crinone®—a vaginal delivery system for progesterone, utilizing a suspension of progesterone in an oil-in-water emulsion, with the polycarbophil swollen to a gel by the water phase. The advantage of this delivery system is that the drug is localized in the vagina, supplying progesterone to the uterus where it is needed. The indications for Crinone are for use in assisted reproductive technology (ART) as well as for menopausal women. Duration of action is claimed to be 24 to 72 h, with the polycarbophil assisting in adhesion to the vaginal wall, and delivering the progesterone locally, from where it travels to the uterus to exert its effect. It is not clear exactly how control of release is achieved in the case of Crinone; the formulation composition suggests that it could be a combination of dissolution control and diffusion control. The contraceptive gel does not require controlled release of nonoxynol 9, as it is a one-use application.

In oral gastrointestinal applications, the efficacy of adhesion in humans of microparticles made of poly(acrylic acid) and polycarbophil continues to be controversial. One study using γ-ray scintigraphic techniques (52) demonstrated that while gastric retention in rats may be enhanced by the use of these polymeric microparticles, no such effect was observed in humans. Previous studies in rats had observed bioadhesion for these polymer particles (53,54). Currently, it is acknowledged that the unique environment of the human GI tract and the composition of its mucin layer may preclude the extrapolation of rat studies to humans, and that no effective bioadhesive works in the human GI tract. Research into this problem continues, and there may be a need for newer types of polymers that exhibit enhanced adhesion.

Several studies in humans have claimed bioadhesive characteristics for hydroxypropylcellulose (55,56) in both nasal and buccal delivery. In the nasal application, duration of action (or of adhesion) is approximately 2–4 h after application of a powder spray, whereas in the buccal application, the best patches adhere only for 30 min to 1 h.

The 3M Company has used a different approach to buccal adhesion. They investigated blends of polyolefins—polyisobutylene (PIB), polyisoprene (PIP), and poly(acrylic acid) (PAA)—and optimized the adhesion based on both invitro (peel strength) and in vivo studies (duration of adhesion). The optimization was directed to development of a removable buccal patch or tablet, which 3M markets under the name of the CyDot® delivery system. From reports of in vivo studies (57), it appears that the adhesive mixture consists of Vistanex® L-100 PIB (8%), Vistanex LMMH PIB (32%), and Polycarbophil poly(acrylic acid) (60%). In dogs, the duration of adhesion appears to be about 12–24 h, while another study using melatonin (58) shows data for 10-h adhesion in human volunteers.

In summary, the following points can be made regarding bioadhesive materials for drug delivery:

1. To date, no effective mucoadhesive has been identified for prolonging GI retention time in humans.
2. Some human data exist for biadhesion of particles delivered intranasally.
3. A much bigger database attests to the viability of buccal adhesion using a variety of polymeric materials

B. Injectable Depot Formulations/Materials and Performance

As mentioned above, all commercially successful depot formulations rely on the use of controlled biodegradation to prolong delivery of active agents. Duration of action ranges from a few weeks to several months. Two companies that are involved in the development of such formulations are TAP Pharmaceuticals and Alkermes. TAP has one line of depot products on the market, for delivery of leuprolide acetate, indicated for prostate cancer. Alkermes has announced preclinical and clinical studies for their products based on ProLease® technology. Both of these technologies utilize polylactide (PLA) or polyglycolide (PGA) in either homopolymer or copolymer form. (PLA is defined as the polylactic acid derived from polymerization of the lactide, and PGA is the polyglycolic acid derived from the glycolide.) Other biodegradable polymers that have been developed include the polyanhydrides (59), poly(ortho esters) (60), and the poly(ε-capralactones) mentioned in Section IV D, all of which have found limited commercial success when compared to the PLA-PGA polymers. Consequently, the discussion in this chapter will focus on the PLA-PGA-based systems.

Polylactide is a stereoregular polymer that occurs in crystalline D or L forms, and is also available as the racemic DL-lactide. The DL form is mostly amorphous with a T_g of about 58°C. The glycolide is available mostly as a semicrystalline material with a T_g of 36°C and T_m of

230°C. The copolymers are amorphous with intermediate T_g values. Biodegradation of all of these polymers is thought to occur via simple hydrolytic cleavage of the ester bond, leading ultimately to the monomeric lactic or glycolic acids, which are metabolized via the Krebs cycle and excreted. Enzymes are speculated to be involved in the cleavage mechanism at later stages of degradation. The rate of degradation is dependent mostly on polymer composition, pH, surface area, and temperature. Therefore, these polymers do not show much variability in degradation rates from one body site to the next, a fact that accounts for their popularity in drug delivery applications.

The range of in vivo biodegradation times is from 2 months for a 50:50 copolymer to about 2 years for a poly(L-lactide). Both fabrication (manipulation of surface area) and polymer composition can be used to obtain a wide range of in vivo duration of action. The commercial product Lupron Depot®, sold by TAP pharmaceuticals, will serve to illustrate this versatility.

Lupron Depot is an injectable formulation of leuprolide acetate that is available in lyophilized microsphere form. It is available in 1-month, 3-month, and 4-month dosages, and is administered via intramuscular injection. Dosages cover the indications of endometriosis and the palliative treatment of prostate cancer. The duration of action (1 month vs. 3 months) is manipulated strictly via the polymer composition. The 1-month injectable formulation contains approximately 75% of poly(DL-lactide-co-glycolide) and 15% D-mannitol as plasticizer, whereas the 3-month formulation contains 75% of poly(DL-lactide) and 15% D-mannitol. Clearly, the copolymer degrades faster in vivo than the poly(DL-lactide), and this accounts for the 1-month and 3-month periods of action. Although not specifically mentioned, the drug is dispersed in the polymer matrix and fabricated into microspheres via any one of the following techniques:

1. Solvent evaporation of an organic phase in water emulsion (useful for water-insoluble drugs)
2. Coacervation processes whereby the polymer is precipitated from an organic phase by addition of an aqueous drug solution (useful for water-soluble drugs)
3. Wurster air suspension coating process involving solution of drug and polymer in an organic solvent (useful for water-insoluble drugs, with the possibility of microcapsule formation)

The other product category where these polymers have been successfully used is the long-acting contraceptive category. Here microcapsules of norethisterone have been fabricated using poly(DL-lactide-co-glycolide) as the membrane material (61). The resulting microcapsules are formulated as a suspension in a sterile saline solution and injected intramuscularly. Up to 3 months of duration of action has been reported in clinical studies (62). These two categories (delivery of low molecular weight peptides and of steroids) continue to attract a lot of attention in the depot formulation attempts. More recent research is focusing on bigger entities such as human growth hormone and interferon.

C. Issues and Opportunities

In the injectable depot field, the major issues areas follow:

1. The lack of suitable polymers besides the PLA-PGA type with clearly defined in vivo degradation rates
2. The capability of delivering a range of proteins and peptides of differing solubility characteristics

The two issues are related in that the second capability is influenced to a large extent by the lack of suitable polymers. The lack of suitable polymers is really a lack of commercialized polymers, since a variety of polymers have been synthesized and studied in laboratories. With the hysteria surrounding breast implants and the liability issues arising from it, most companies have been reluctant to undertake large-scale manufacturing of suitable polymers. Remarks attributed to the implant field are equally applicable here in terms of opportunities for biomaterial suppliers

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